2.1 Non-Technical Abstract

An American male dies of prostate cancer every 14 minutes, 39,200 men/year. While surgery or radiation can cure early-stage prostate cancer confined to the prostate, no curative therapy exists after surgery or radiation for the reccurence of local disease. History has shown that recurrent local disease has already developed undetectable micro-metastasis. The target population of this study is patients with locally recurrrent disease. The ten year overall survival rate for patients with locally recurrent disease is 35%, for the disease invariably progresses with metastasis to bone. The standard of care for patients who experience a recurrence following surgery or radiotherapy is simply supportive therapy, followed by drugs to reduce the bone pain of metastasis, or treatment with investigational therapies.

The rationale for this clinical trial of CN706 translates from 4 years of research at Calydon, Inc. and from NIH-sponsored research at the Johns Hopkins Oncology Center. Prostate-specific antigen (PSA) is found in over 95% of prostate cancers and forms the basis of the most widely used diagnostic marker of disease progression in all of cancer. DNA sequences containing the regulatory elements that control where PSA is made in the body have been inserted into the adenovirus 5 (Ad5) genome so as to drive the expression of a gene necessary for Ad5 replication. The resultant virus, CN706, is restricted in its replication to PSA-expressing cells, prostate cancer cells. Thus, CN706 is a therapy using a virus designed specifically to replicate in and kill prostate cancer cells.

Peer-reviewed, preclinical studies have confirmed that CN706 results in selective cytotoxicity towards PSA-expressing cells both in cell culture and animal models. A single direct injection of CN706 into tumors in animal models resulted in the regression of large (1 cm diameter, 5% of the body weight of a mouse) prostate cancer tumors within 5 weeks and led to the elimination of serum PSA levels. No treatment-related deaths were seen in preclinical toxicology studies of the intraperitoneal and intraprostatic administration of CN706. As would be expected for Ad5, no evidence of germ-line transmission of CN706 was detected. No abnormalities in histology were noted following the direct injection of CN706 into the prostate.

The IND for this proposed single-center, non-randomized, open-label, Phase I dose-escalation study of the direct injection of CN706 into the prostate has been reviewed by the FDA and is active. With the concurrence of the FDA, the primary objective of the study will be to determine the maximum tolerated dose of CN706 using NCI common toxicity criteria. Secondary objectives include evaluation of antitumor activity and time to disease progression.

CN706 will be administered using the standard of care for the placement of radioactive seed implants for radiotherapy of the prostate (brachytherapy). The methodology includes definition and location of the prostate, treatment planning based on prostate volume, and direct injection into the prostate using ultrasound guidance. Patients under spinal anesthesia will receive 10 intraprostatic injections of CN706 on Day 1 of the study, whereas 20-40 injections are commonly employed for the placement of the radioactive seed implants. The dose levels to be tested in this study are consistent with dose levels at which efficacy was seen in animal studies and are supported by the results of animal toxicology studies. The starting dose level for the trial is 100-fold lower than the no-effect dose of CN706 administered intraperitoneally to rats and 50-fold lower than the lowest dose of CN706 administered directly into the prostate of rats. Three patients will be treated at each of five dose levels in increasing half log dose increments. Direct injection of CN706 directly into the prostate offers the potential of specifically targeting the cell killing ability of adenovirus uniquely to prostate cancer cells.